

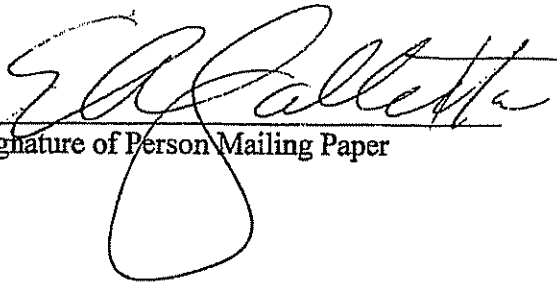
EXHIBIT A

CERTIFICATION UNDER 37 CFR §1.10

I hereby certify that this Reissue Application Transmittal and the documents referred to as enclosed therein are being deposited with the United States Postal Service on this date, March 4, 2005 in an envelope marked "Express Mail" Mailing Label No. EV 544765920 US, addressed to Mail Stop Reissue, Commissioner for Patents, P. O. Box 1450, Alexandria, Virginia 22313-1450.

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- Reissue Patent Application Transmittal – Form PTO/SB/50
- Reissue Application Fee Transmittal Form – Form PTO/SB/56 (Two copies)
- Amendment under 37 CFR §1.173(b) (including Statement under 37 CFR §1.173(c))
- Reissue Oath/Declaration (Unsigned)
- Reissue Patent Application, consisting of copy of U.S. Patent No. 6,528,784, including:
 - Specification
 - Drawings (8 Figures)
 - Claims
 - Certificate of Correction
- Power of Attorney (with attached statement under 37 CFR §3.73(b))
- Written Consent of Assignee
- Statement under 37 CFR §3.73(b)
- Statement under 37 CFR §1.178(b)
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PTO/SB/50 (09-04)

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REISSUE PATENT APPLICATION TRANSMITTAL

Address to: Mail Stop Reissue Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450	Attorney Docket No.	102718-300
	First Named Inventor	Keqi Tang, et al.
	Original Patent Number	U.S. Patent No. 6,528,784
	Original Patent Issue Date (Month/Day/Year)	03/04/03
	Express Mail Label No.	EV 544765920 US

APPLICATION FOR REISSUE OF:

(Check applicable box)



Utility Patent



Design Patent



Plant Patent

APPLICATION ELEMENTS (37 CFR 1.173)

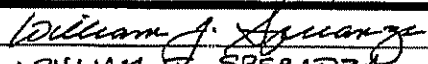
1. ☒ Fee Transmittal Form (PTO/SB/56) (Submit a duplicate copy)
2. ☐ Applicant claims small entity status. See 37 CFR 1.27.
3. ☒ Specification and Claims in double column copy of patent format (amended, if appropriate)
4. ☒ Drawing(s) (proposed amendments, if appropriate)
5. ☒ Reissue Oath/Declaration (original or copy) (37 C.F.R. 1.175) (PTO/SB/51 or 52) (unsigned)
6. ☒ Power of Attorney
7. ☒ Original U.S. Patent currently assigned? ☒ Yes ☐ No
(If Yes, check applicable box(es))
☒ Written Consent of all Assignees (PTO/SB/53)
☒ 37 CFR 3.73(b) Statement (PTO/SB/96)
8. ☐ CD-ROM or CD-R in duplicate, Computer Program (Appendix) or large table
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 - a. ☐ Computer Readable Form (CRF)
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 - i. ☐ CD-ROM (2 copies) or CD-R (2 copies); or
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 - c. ☐ Statements verifying identity of above copies

ACCOMPANYING APPLICATION PARTS

10. ☒ Statement of status and support for all changes to the claims. See 37 CFR 1.173(c).
11. ☐ Foreign Priority Claim (35 U.S.C. 119) (if applicable)
12. ☐ Information Disclosure Statement (IDS) PTO/SB/08 or PTO-1449
☐ Copies of citations attached
13. ☐ English Translation of Reissue Oath/Declaration (if applicable)
14. ☒ Preliminary Amendment
15. ☒ Return Receipt Postcard (MPEP 503) (Should be specifically itemized)
16. ☒ Other:
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This collection of information is required by 37 CFR 1.173. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Mail Stop Reissue, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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REISSUE APPLICATION FEE TRANSMITTAL FORM							Docket Number (Optional) 102718-300	
Application as Filed - Part 1								
	(1) Claims In Patent	(2) Claims Filed In Reissue Application	(3) Number Extra	Small Entity		Other than a Small Entity		
				Rate (\$)	Fee (\$)		Rate (\$)	Fee (\$)
Total Claims (37 CFR 1.16(i))	(A) 9	(B) 42	**** 22 =	x	=		x 50 =	1100.00
Independent Claims (37 CFR 1.16(h))	(C) 4	(D) 11	* 8 =	x	=		x 200 =	1600.00
Application Size Fee (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$250 (\$125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						or	0.00
					Filing Fee (37 CFR 1.16(e))			300.00
					Search Fee (37 CFR 1.16(n))			500.00
					Examination Fee (37 CFR 1.16(r))			600.00
					Total Filing Fee			4100.00
Application as Amended - Part 2								
	(1) Claims Remaining After Amendment	(2) Highest Number Previously Paid For	(3) Extra Claims Present	Small Entity		Other than a Small Entity		
				Rate (\$)	Fee (\$)		Rate (\$)	Fee (\$)
Total Claims (37 CFR 1.16(i))	***	MINUS	**	=	X	=	x	=
Independent Claims (37 CFR 1.16(h))	***	MINUS	*****	=	x	=	x	=
Application Size Fee (37 CFR 1.16(s))	If the specification and drawings exceed 100 sheets of paper, the application size fee due is \$250 (\$125 for small entity) for each additional 50 sheets or fraction thereof. See 35 U.S.C. 41(a)(1)(G) and 37 CFR 1.16(s).						or	
					Total Additional Fee			

* If (D) is less than (C), enter "0" in column 3. For reissues filed on or after Dec. 8, 2004, enter (D) minus 3 or "0" if (D) is less than 3.
 ** If the "Highest Number of Total Claims Previously Paid For" is less than 20, enter "20" in this space.
 *** After any cancellation of claims.
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 For amendments filed prior to Dec. 8, 2004, enter the higher of the Number Previously Paid or Number of Independent Claims in Patent.

☐ Applicant claims small entity status. See 37 CFR 1.27.

☒ Please charge Deposit Account No. 23-1665 in the amount of \$4,100.00
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☒ The Director is hereby authorized to charge any additional fees under 37 CFR 1.16 or 1.17 which may be required, or credit any overpayment to Deposit Account No. 23-1665. A duplicate copy of this sheet is enclosed.

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William J. Speranza
Signature

William J. Speranza
Typed or printed name

3/4/05
Date

26,340
Registration Number, if applicable

203-498-4400
Telephone Number

This collection of information is required by 37 CFR 1.16. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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REISSUE PATENT APPLICATION OF
U.S. Patent No. 6,528,784

Entitled

MASS SPECTROMETER SYSTEM INCLUDING A DOUBLE ION GUIDE
INTERFACE AND METHOD OF OPERATION

To:
Keki Tang
Alan E. Schoen
Jean-Jacques Donyach



US006528784B1

(12) **United States Patent**
Tang et al.

(10) Patent No.: **US 6,528,784 B1**
(45) Date of Patent: **Mar. 4, 2003**

(54) **MASS SPECTROMETER SYSTEM
INCLUDING A DOUBLE ION GUIDE
INTERFACE AND METHOD OF OPERATION**

5,852,294 A 12/1998 Gulcicek et al. 250/292
6,015,972 A 1/2000 Hager 250/282
6,107,623 A 8/2000 Baleman et al. 250/282

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(*) Notice: Subject to any disclaimer, the term of this
patent is extended or adjusted under 35
U.S.C. 154(b) by 49 days.

(21) Appl. No.: 09/715,815

(22) Filed: Nov. 16, 2000

Related U.S. Application Data

(63) Continuation-in-part of application No. 09/454,273, filed on
Dec. 3, 1999, now abandoned.

(51) Int. Cl.⁷ B01D 59/44; H01J 49/00

(52) U.S. Cl. 250/282

(58) Field of Search 250/282

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5,179,278 A 1/1993 Douglas 250/290
5,432,343 A 7/1995 Gulcicek et al. 250/288
5,652,427 A * 7/1997 Whitehouse et al. 250/282
5,811,800 A 9/1998 Franzen et al. 250/288

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Primary Examiner—Jack Berman

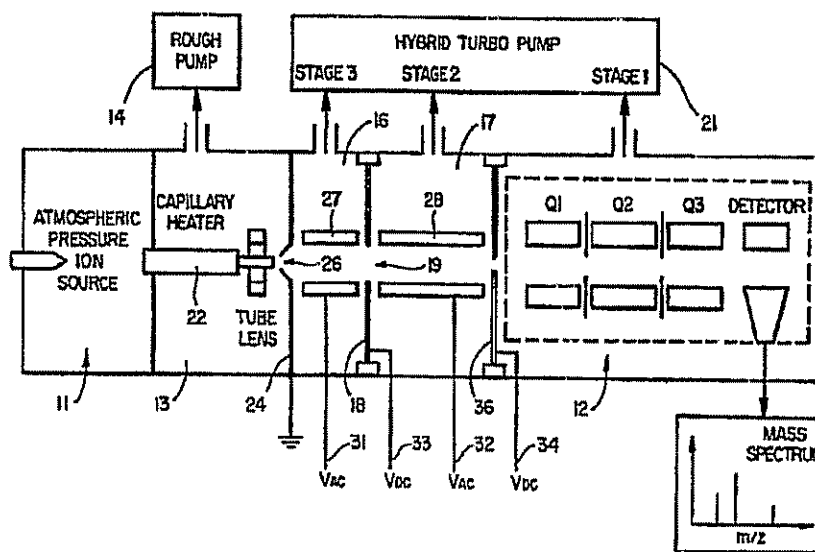
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(57) **ABSTRACT**

There is described an interface for delivering ions generated
in an ion source into a mass analyzer in a chamber under
vacuum pressure. In particular, the interface employs two
consecutive ion guides operated to dissociate adduct ions
formed in the ion source or high pressure regions of the
interface between the ion source and the mass analyzer, thus
improving the limit of detection or limit of quantitation of
the mass analyzer by increasing the analyte ion current.

9 Claims, 8 Drawing Sheets



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- Hagg, Conny and Szabo et al., "New Ion-Optical Devices Utilizing Oscillatory Electric Fields. IV. Computer Simulations of the Transport of an Ion Beam Through an Ideal Quadrupole, Hexapole, and Octopole Operating in the RF-Only Mode", *Int. J. Mass Spectrometry and Ion Processes*, 73 (1986) 295-312.
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MASS SPECTROMETER SYSTEM INCLUDING A DOUBLE ION GUIDE INTERFACE AND METHOD OF OPERATION

RELATED APPLICATIONS

This application is a continuation-in-part-of and claims priority to pending application Ser. No. 09/454,273 filed Dec. 3, 1999 now abandoned.

FIELD OF THE INVENTION

This invention relates generally to mass spectrometry, and more particularly to mass spectrometers employing atmospheric pressure ion sources such as electrospray or atmospheric pressure chemical ionization. More particularly, the invention relates to the use of two consecutive ion guides between the ion source and the mass analyzer to dissociate adduct ions, thus increasing the ion current for the analytically useful molecular species.

BACKGROUND OF THE INVENTION

Generally, the interface between the atmospheric pressure ion source and the mass analyzer includes a capillary tube or other restrictive aperture which determines ion and gas throughput between the atmospheric pressure ionization region and a lower pressure region. The ions are drawn through the capillary or other restrictive aperture and directed to a downstream conical skimmer with a small aperture through which the sample ions flow. A tube lens or other electrostatic or electrodynamic focusing element may be associated with the capillary to force ions to the center of the jet stream leaving the capillary to thereby increase the ion transmission through the aperture of the skimmer. Reference is made to U.S. Pat. No. 5,157,260 which describes the operation of an atmospheric pressure ionization source, capillary lens and conical skimmer. One or more vacuum stages are interposed between the skimmer and the mass analyzer which is operated at vacuum pressures in the free molecular flow region.

The prior art interface vacuum stages have included ion guides to transfer the ions through the stages of decreasing pressure into the mass analyzer. In many prior art systems, the ions are guided by electrostatic lenses. In other systems, the ions are guided by electrodynamic multipole ion guides.

The use of an r.f.-only octopole ion guide for focusing and guiding ion beams has been described by Teloy and Gerlich (Chem. Phys., Vol. 4, p. 417, 1974) and Jarrold et al. (Mol. Phys., Vol. 39, p. 787, 1980).

The dissociation of mass-selected ions in an r.f.-only quadrupole by collision with a target gas at low translational energies ($E_{\text{lab}} < \text{about } 100 \text{ eV}$) has been described by R. A. Yost and C. G. Enke et al. (Anal. Chem., Vol. 51, p. 1251a, 1979), and Dawson et al. (Int. J. Mass Spec. Ion Proc., Vol. 42, p. 195, 1982).

McIver et al. described the use of an r.f.-only quadrupole ion guide for guiding a beam of mass-selected ions into a Fourier-transform ion cyclotron resonance mass analyzer (Int. J. Mass Spec. Ion Proc., Vol. 64, p. 67, 1985).

Szabo described the theory of operation for multipole ion guides with various electrode structures (Int. J. Mass Spec. Ion Proc., Vol. 73, pp. 197-312, 1986).

Efficient transport of ions through vacuum chambers by multipole ion guides has been described by Smith et al. (Anal. Chem., Vol. 60, pp. 436-441, 1988).

Beu et al. described the use of three quadrupole ion guides to transport ions from an atmospheric pressure ion-

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ization source through three vacuum pumping stages into a Fourier-transform ion cyclotron resonance mass analyzer (J. Am. Soc. Mass Spec., Vol. 4, pp. 557-565, 1993).

U.S. Pat. No. 4,963,736 describes the use of a multipole ion guide in the first pumping stage of a two-stage system. Operation of the multipole ion guide in certain length-times-pressure regimes is claimed for the purposes of enhancing ion signal.

U.S. Pat. Nos. 5,179,278 and 5,811,800 describe the temporary storage of ions in an r.f. multipole rod system for subsequent analysis in an r.f. quadrupole ion trap mass spectrometer. This is done for the purpose of matching the time scales of compounds eluting from chromatographic or electrophoretic separation devices to the time scale of mass spectrometric analyses performed by an r.f. quadrupole ion trap.

U.S. Pat. No. 5,432,343 describes an ion focusing lensing system for interfacing an atmospheric pressure ionization source to a mass spectrometer. It describes the use of an electrostatic lens in a transition flow pressure region of the interface, claiming benefit of independent adjustment of operating voltages controlling the collisionally induced dissociation and declustering processes. Enhancement of ion beam transmission into the mass analyzer is also claimed.

U.S. Pat. No. 5,652,427 describes in one embodiment a system in which a multipole ion guide extends between two vacuum stages and in another embodiment a system which includes a multipole in each of two adjacent stages. Improved performance and lower cost are claimed.

U.S. Pat. No. 5,852,294 describes the construction of a miniature multipole ion guide assembly.

A goal to be achieved in all single or multiple interface vacuum chambers is to transport as many protonated molecular cations or molecular anions as possible from the atmospheric pressure ionization source to the mass analyzer. However, many solvent adduct ions which are formed in the high pressure region travel through the interface vacuum chambers into the analyzer. The process of solvent adduction in the mass spectrometer system is generally considered to be a non-covalent association between sample ions of interest and neutral solvent molecules. Thus, in the case of introduction of an analyte into an electrospray or atmospheric pressure chemical ionization source, the ion current produced from that analyte may be divided between the protonated molecular cation or molecular anion and one or more solvent adduct species. Specific detection is usually accomplished by monitoring the ion signal, or derivative of that signal, for one specific mass. In the case where solvent adducts are formed, the limit of detection or limit of quantitation for the analyte is reduced.

Experimental evidence indicates that these adduct ions are predominantly formed in the high pressure regions of the system ranging from the API source region through the interface vacuum regions. The degree of adduction varies directly with the pressures in these regions. The formation of adduct ions significantly reduces the abundance of sample analyte ions. Furthermore, the adduct ions which enter into the mass analyzer complicates the mass spectrum and make the identification of mass peaks more difficult.

OBJECTS AND SUMMARY OF THE INVENTION

It is an object of the present invention to provide a mass spectrometer system employing an ion source with multiple ion guides configured and operated to convert adduct ions into sample ions and a method of operating multiple ion

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guides to convert adduct ions into sample ions to thereby increase the analyte ions current and sensitivity of the mass spectrometer system.

In accordance with the invention, there is provided a mass spectrometer including a mass analyzer disposed in a high vacuum chamber for analyzing ions formed in an ionization source which includes first and second evacuated interface chambers immediately preceding the mass analyzer chamber, with the first interface chamber being at a higher pressure than the second interface chamber, and including a first ion guide for guiding ions from the ion source into said second interface chamber which includes a second multipole ion guide for guiding the ions from the first interface chamber into the high vacuum analyzer chamber for analysis. Both r.f. and DC potentials are applied to the said first and second ion guides to ensure ion focusing and transmission through related vacuum chamber. A first ion lens is disposed at the input of the first interface chamber for directing ions into the first multipole ion guide, an inter-chamber ion lens is disposed between the first and second interface chambers for directing ions into said second multipole ion guide, and an ion lens or a lens stack is disposed between the second interface chamber and the analyzer chamber for directing ions into said analyzer for analysis. These ion lenses also serve as gas conductance restrictors between said interface chambers.

A DC voltage source is connected to provide a potential difference between the first lens and the first multipole ion guide or between interchamber lens and the second multipole ion guide or both which defines the ion's translational kinetic energy as it enters the second multipole ion guide. The ion's translational kinetic energy is chosen such that at the vacuum pressure of the second interface chamber adduct ions are converted into sample ions by collision induced dissociation without fragmentation of sample ions whereby the sample ion current entering the analyzer is increased, thereby increasing the sensitivity of the mass spectrometer system.

There is provided a method of mass analyzing ions produced in an atmospheric pressure ionization source in which adduct ions formed in the mass spectrometer system are dissociated prior to analysis to increase the analyte ion current to the mass analyzer and the sensitivity of the mass spectrometer system.

There is provided a method of operating a mass spectrometer system in which an analyzer in a vacuum chamber analyzes ions formed in an atmospheric pressure ionization source. The system includes first and second multipole ion guides disposed in serial first and second evacuated chambers immediately preceding the analyzer. The method comprises applying a DC voltage between the ion lens preceding either the first or the second multipole ion guide to provide translational kinetic energy to the adduct ions sufficient to dissociate any adduct ions at the pressure of the second chamber without fragmenting the sample ions whereby to increase the sample ion current directed into the analyzer and the sensitivity of the mass spectrometer system.

BRIEF DESCRIPTION OF THE DRAWINGS

The foregoing and other objects of the invention will be more clearly understood from the following description when read in conjunction with the accompanying drawings in which:

FIG. 1 is a schematic view of a mass spectrometer system including an atmospheric pressure ion source coupled to a tandem mass analyzer through evacuated interface chambers with multipole ion guides.

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FIGS. 2A and 2B show the mass spectra for an injection of Alprazolam in a liquid stream flowing at 400 microliters per minute ($\mu\text{l}/\text{min}$) with -5 VDC offset and -5 VDC offset applied to the second ion guide.

FIGS. 3A and 3B show the mass spectra for an injection of Alprazolam in a liquid stream flowing at 1 milliliter per minute (ml/min) with -5 VDC offset and -15 VDC offset applied to the second ion guide.

FIGS. 4A and 4B show the mass spectra for an injection of codeine-d3 in a liquid stream flowing at 400 $\mu\text{l}/\text{min}$ with -5 VDC offset and -15 VDC offset applied to the second ion guide.

FIGS. 5A and 5B show the mass spectra for an injection of codeine-d3 in a liquid stream flowing at 1 ml/min with -5 VDC offset and -15 VDC offset applied to the second ion guide.

FIGS. 6A and 6B show the mass spectra for an injection of acetaminophen in a liquid stream flowing at 400 $\mu\text{l}/\text{min}$ flow with -5 VDC offset and -15 VDC offset applied to the second ion guide.

FIGS. 7A and 7B show the mass spectra for an injection of Ibuprofen in a liquid stream flowing at 400 $\mu\text{l}/\text{min}$ with $+5$ VDC offset and $+15$ VDC offset applied to the second ion guide.

FIG. 8 is a schematic view of a mass spectrometer system as in FIG. 1 with a single quadrupole mass analyzer rather than a tandem mass analyzer or other suitable mass analyzer.

DESCRIPTION OF PREFERRED EMBODIMENTS

Referring to FIG. 1, an atmospheric pressure ion source in chamber 11 is interfaced to a tandem mass analyzer 12 via three vacuum pumping stages. The first stage 13 which has the highest pressure is evacuated by an oil-filled rotary vane vacuum pump 14. Other types of vacuum pumps may also be used for this stage, such as a diaphragm pump or scroll pump. A typical pressure for first stage 13 is between 1 and 2 Torr. The second and third stages 16 and 17 are separated by a lens 18 with an orifice 19, which in one example was 1.5 mm in diameter, and can be evacuated by a hybrid or compound turbomolecular pump 21 which includes both turbomolecular and molecular drag pumping stages, and may have multiple inlets into each of these pumping stages, or by individual vacuum pumps (not shown). As will be explained in accordance with the present invention, the pressure in chamber 16 is below 500 mTorr, preferably below 250 mTorr, and more preferably below 175 mTorr; and the pressure in chamber 17 is below 1 mTorr, preferably below 0.7 mTorr, and more preferably below 0.5 mTorr. The pressure in the tandem mass analyzer chamber is approximately 1×10^{-5} Torr or below.

The atmospheric pressure ion source may be an electrospray ion source or atmospheric pressure chemical ionization source. With either ion source, sample liquid is introduced into the chamber 11, which is at atmospheric pressure, and ionized. The ions are drawn through a capillary 22, which may be heated, into chamber 13. The end of the capillary is opposite a conical skimmer 24 which includes a central orifice or aperture 26. The skimmer separates the low pressure stage 13 from the lower pressure stage 16. A portion of the ion and gas flow is skimmed from the free jet expansion leaving the capillary and enters the second lower pressure stage. The ions which travel through the skimmer are guided into the mass analyzer by first and second multipole ion guides 27 and 28. In one example, the ion guides are square quadrupoles. The guide 27 is 1.25 inches

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long and the guide 28 is 3.37 inches with the rods separated by 0.118 inches (3 mm). The ion guides are mounted coaxially using polycarbonate holders (not shown). The quadrupole ion guides are operated by applying AC voltages 31 and 32 to the poles which guide ions as is well known. Ions which enter the second and third stages drift under the influence of DC voltage 33 applied between the skimmer lens 24 and lens 18, by DC voltage 34 applied between the lens 18 and the lens 36, and by DC offset voltages applied to ion guides 27 and 28.

As discussed above, solvent adduct ions are formed in the high pressure regions ranging from the atmospheric pressure region to the quadrupole ion guide stages or regions. The degree of adduction is believed to vary directly with the pressure in these regions. The formation of adduct ions can significantly reduce the abundance of sample analyte ions which reach the analyzer. Consequently, effective conversion of the adduct ions into protonated molecular cations or molecular anions can greatly enhance the sample ion current and the sensitivity of the mass spectrometer system.

We have discovered that the solvent adduct ions can be dissociated and converted into sample ions in the second ion guide 28 by applying a small DC offset voltage between the ion guide 28 and the lens 18 to increase the energy of the solvent adduct ions. An additional 10 volts DC offset applied to the second ion guide (usually used with a standard 5 V DC offset) is sufficient to convert the solvent adducts into the protonated molecular cation or molecular anion for all compounds tested. In addition, this offset voltage is insufficient to cause fragmentation of the analyte ions at the pressure of the second stage.

Both pumping efficiency and solvent adduction were evaluated. The pumping requirement and vacuum condition on the double ion guide system were compared to a standard TSQ 7000 system sold by ThermoQuest Corporation under the same gas load conditions. Several different compounds including a) acetaminophen; b) Alprazolam; c) codeine-d3; d) ibuprofen were used to investigate the degree of solvent adduction, conversion to protonated molecular cation or molecular anion, and fragmentation of the protonated molecular cation or molecular anion. The solvent used in the experiment was 50:50 acetonitrile:water+5mM ammonium acetate adjusted to a pH of 4.5. Table 1 lists the main experimental conditions, compound, molecular weight and type of solvent adduction investigated.

TABLE 1

Compound	Molecular Weight	Solvent Adduct	Ion Polarity	LC Flow (μ /min)	Sample Injected (ng)
Acetaminophen	151	Acetonitrile	Positive	400	500
Alprazolam	308	Acetonitrile	Positive	400-1000	1.6
Codeine-d3	302	Acetonitrile	Positive	400-1000	50
Ibuprofen	206	Acetate	Negative	200	50

FIGS. 2-7 show the comparative mass spectra for the four different compounds used in the evaluation under standard (± 5 V DC) offset and an incremental 10 V DC (± 15 V DC total) offset conditions between the interstage ion lens 18 and the second multipole ion guide 28 indicating that the signal intensity and peak area for the protonated molecular cations or molecular anions can be significantly enhanced by the application of the increased DC offset on the second multipole ion guide 28.

FIG. 2A shows the mass scan for Alprazolam at 400 μ l/min liquid chromatograph flow with the standard ± 5 volt

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offset, and FIG. 2B shows Alprazolam with an incremental 10 volts of offset at the same flow rate. The increased sample ion signal produced by the incremental offset voltage is apparent.

FIGS. 3A and 3B show the mass spectra for Alprazolam at 1 ml/min flow. Again the increased sample ion current is apparent. FIGS. 4A and 4B show the mass spectra for codeine-d3 at 400 μ l/min flow with the standard and increased offset voltages. The increased sample ion signal at m/z 302 is apparent. The same mass spectra are shown for 1 ml/min codeine-d3 in FIGS. 5A and 5B. FIGS. 6A and 6B show a comparison of the mass spectra for Acetaminophen at 400 μ l/min flow with the standard and increased offset voltages. Again, the vast improvement in sensitivity is apparent. FIGS. 7A and 7B show the mass spectra for ibuprofen flowing at 400 μ l/min flow with the standard and increased offset voltages. The improved signal at m/z 205 should be noted.

The DC offset required for high efficiency solvent adduct ion conversion at different vacuum conditions in both first chamber and second chamber was also investigated. The following tables summarize one set of tests in which the ratio of the acetonitrile adduct to the protonated molecular cation of codeine-d3 was investigated at different pressures and different DC offset voltages on the second ion guide.

TABLE 2

DC offset on second ion guide (volts)	-5	-5	-5	-5	-5
First ion guide pressure (mTorr)	609	563	502	224	167
Second ion guide pressure (mTorr)	1.6	1.2	1	0.7	0.5
Ratio of acetonitrile adduct ion to protonated molecular ion	704%	526%	288%	354%	248%
DC offset on second ion guide (volts)	-15	-15	-15	-15	-15
First ion guide pressure (mTorr)	609	563	502	224	167
Second ion guide pressure (mTorr)	1.6	1.2	1	0.7	0.5
Ratio of acetonitrile adduct ion to protonated molecular ion	445%	407%	82%	38%	17%
DC offset on second ion guide (volts)	-35	-35	-35	-35	-35
First ion guide pressure (mTorr)	609	563	502	224	167
Second ion guide pressure (mTorr)	1.6	1.2	1	0.7	0.5
Ratio of acetonitrile adduct ion to protonated molecular ion	300%	248%	40%	7%	3%

The bold data in Table 2 indicates the range of pressure and offset voltages at which the most efficient conversion of solvent adduct to protonated molecular cation is achieved. According to these results, the operating pressure for the ion guides should be:

First Ion Guide: below 500 mTorr

Second Ion Guide: below 1 mTorr and above 0.1 mTorr

Although the offset voltage which provides the translational kinetic energy to the adduct ions has been described as applied between the interstage lens and the second multipole guide, it is apparent that the translational kinetic energy can be provided by applying the DC offset voltage between the skimmer lens and the first multipole stage or by applying voltages simultaneously between each lens and its respective multipole ion guide. The operating pressure will be the same as above.

The DC offset voltage range for efficient solvent adduction conversion should be ± 10 to ± 30 Volts, although ± 10 V is preferable.

The preferred pressure range is less than 250 mTorr for the first stage and 0.7 mTorr for the second stage, and the most preferred pressure range is less than 175 mTorr for the first stage, and 0.5 mTorr for the second stage.

The present invention can be used for other types of mass analyzers such as quadrupole mass analyzers of the type

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described in U.S. Pat. No. 4,540,884 and U.S. Pat. No. RE 34,000. FIG. 8 shows the interface stages and ion guides associated with a quadrupole mass analyzer 41 disposed in the vacuum chamber 12. Like members have been applied to the parts which correspond to those in FIG. 1. It is apparent that the invention is applicable to other types of mass analyzers such as quadrupole ion trap, ion cyclotron resonance (i.e., magnetic ion trap), time-of-flight, magnetic sector, and double-focusing magnetic/electric sector, monopole, etc.

What is claimed is:

1. A mass spectrometer system including a mass analyzer disposed in a high vacuum chamber for analyzing sample ions formed at atmospheric pressure and directed to the analyzer through intermediate vacuum chambers in which sample ions and solvent molecules form adduct ions with a reduction of sample ion current including:

first and second evacuated chambers directly preceding the mass analyzer chamber with the first chamber being at a higher pressure than the second chamber,

a first multipole ion guide in the first chamber for guiding ions into said second chamber,

a second multipole ion guide in the second chamber for guiding ions from the first chamber into the high vacuum chamber for mass analysis, and

means associated with one or both of said first and second multipole ion guides for increasing the translational kinetic energy of the adduct ions so that at the vacuum pressure of the second interface chamber adduct ions traveling into the chamber are converted into sample ions without fragmentation of sample ions whereby to increase the sample ion current and therefore the sensitivity of the mass spectrometer system.

2. A mass analyzer as in claim 1 including ion lenses preceding each said multipole ion guide and a DC voltage is applied between a selected lens and its associated ion guide to increase the translational kinetic energy of the adduct ions entering the second interface chamber.

3. A method of mass analyzing sample ions produced at atmospheric pressure and introduced into a mass analyzer disposed in a vacuum chamber, and in which some sample ions and solvent molecules combine to form adduct ions with a reduction of sample ions comprising the step of dissociating the adduct ions prior to entry into the mass analyzer to form sample ions to increase the sample ion current entering into the mass analyzer.

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4. The method of operating a mass spectrometer system including a mass analyzer which analyzes sample ions formed at atmospheric pressure, and in which some sample ions and solvent molecules combine to form adduct ions with a reduction of sample ions, said system including first and second multipole ion guides disposed in serial first and second evacuated chambers separated by an ion lens for guiding analyte ions into said mass analyzer and an ion lens defining the first evacuated chamber which comprises

applying a DC offset voltage between a selected one or both lenses and the succeeding multipole ion guide having an amplitude so as to provide translational kinetic energy to said adduct ions to dissociate the adduct ions without dissociating sample ions at the pressure of the second chamber to increase the sample ion current and the sensitivity of the mass spectrometer system.

5. A mass spectrometer system as in claim 4 in which the pressure in the first chamber is below 500 mTorr, and in the second chamber is below 1 mTorr, and the offset voltage applied between the interchamber lens and the second multipole ion guide is between ± 10 volts and ± 30 volts.

6. A mass spectrometer system as in claim 5 in which the pressure in the first chamber is less than 250 mTorr, and in the second chamber is less than 0.7 mTorr.

7. A mass spectrometer system as in claim 5 in which the pressure in the first chamber is less than 175 mTorr, and in the second chamber is less than 0.5 mTorr.

8. A mass spectrometer as in claim 6 or 7 in which the offset voltage is ± 10 volts.

9. The method of analyzing ions in a mass analyzer which includes a first chamber maintained at a first pressure and a second chamber maintained at a lower pressure comprising the steps of:

forming sample ions at atmospheric pressure with some of the sample ions combining with solvent ions to form adduct ions,

guiding said sample ions and adduct ions through at least a first chamber maintained at a first pressure and a second chamber maintained at a lower pressure,

adding translational kinetic energy to said adduct ions as they travel through said chambers such that in the second chamber the adduct ions are dissociated without fragmenting the sample ions prior to entering the mass analyzer.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 6,528,784 B1
DATED : March 4, 2003
INVENTOR(S) : Tang et al.

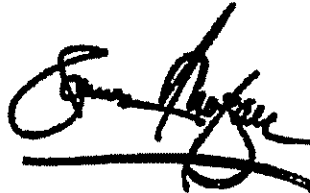
Page 1 of 1

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page

After Item [76], insert -- [73] Assignee: Thermo Finnigan LLC, San Jose, California --

Signed and Sealed this
Sixteenth Day of December, 2003

A handwritten signature in black ink, appearing to read "James E. Rogan", written over a horizontal line.

JAMES E. ROGAN
Director of the United States Patent and Trademark Office

U.S. Patent

Mar. 4, 2003

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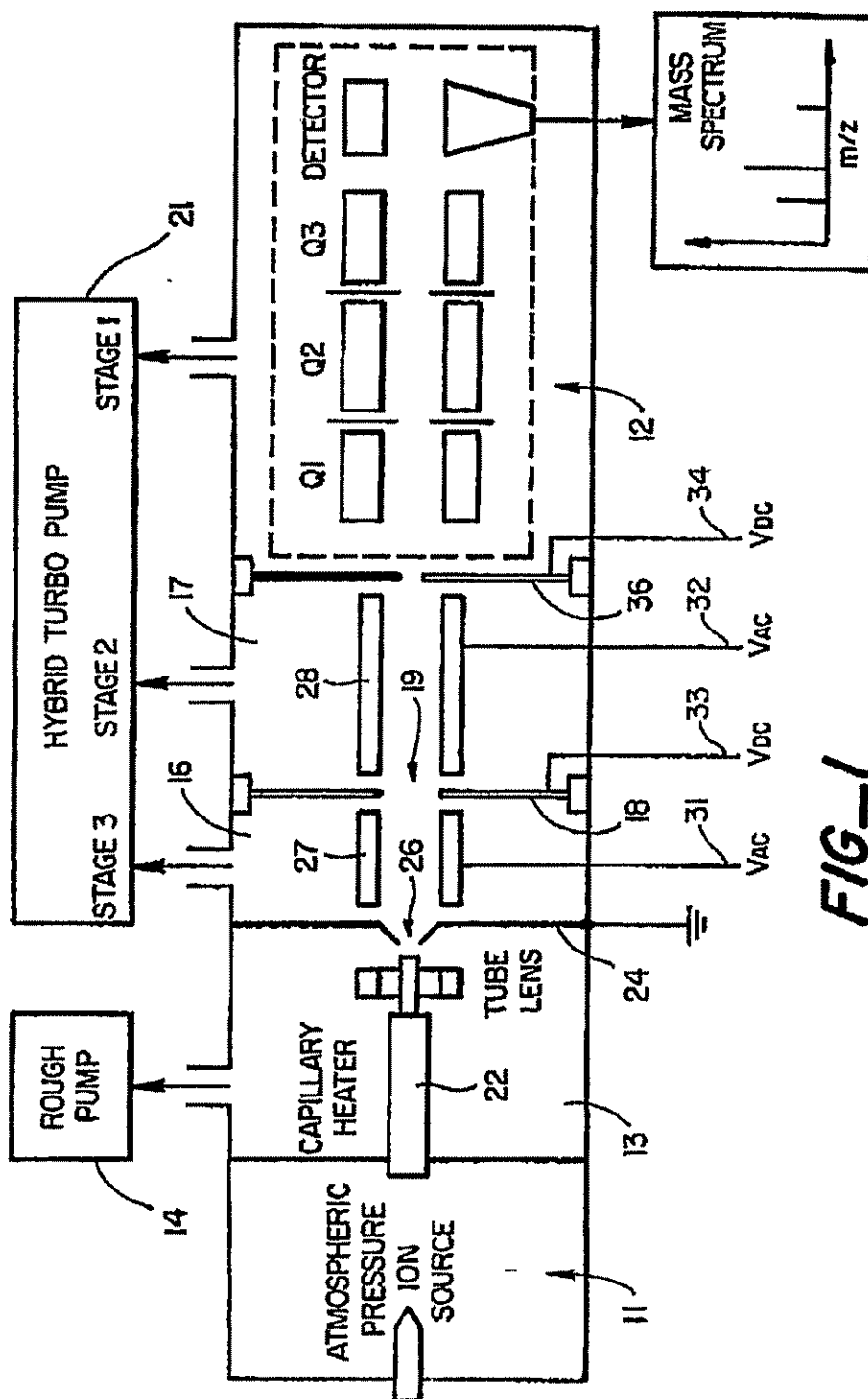


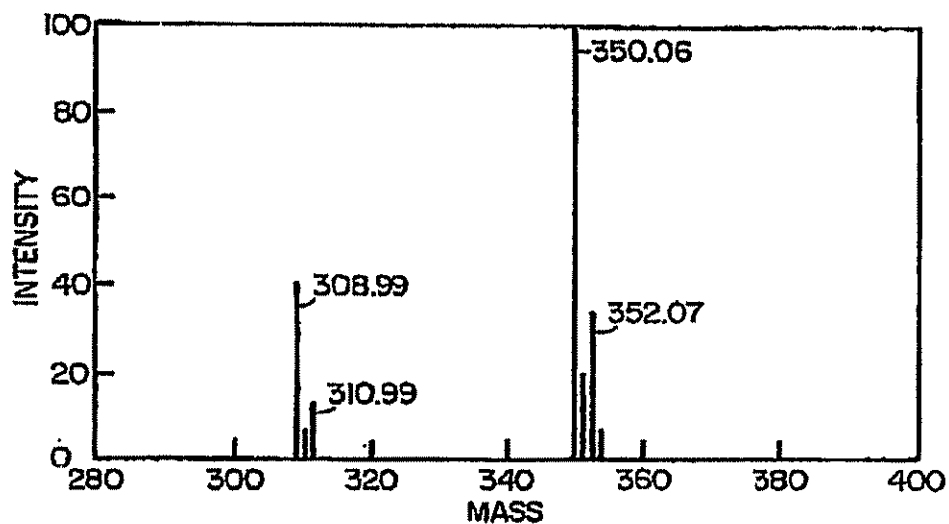
FIG. 1

U.S. Patent

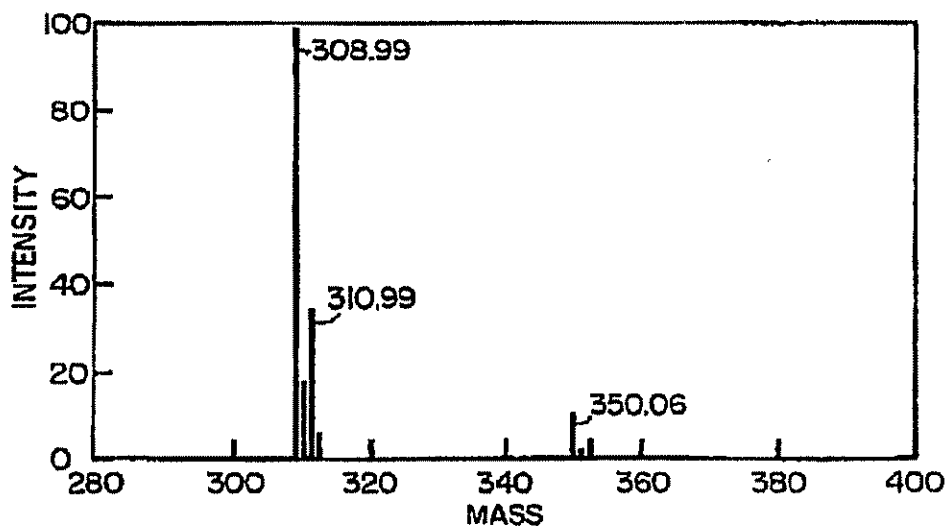
Mar. 4, 2003

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FIG_2A



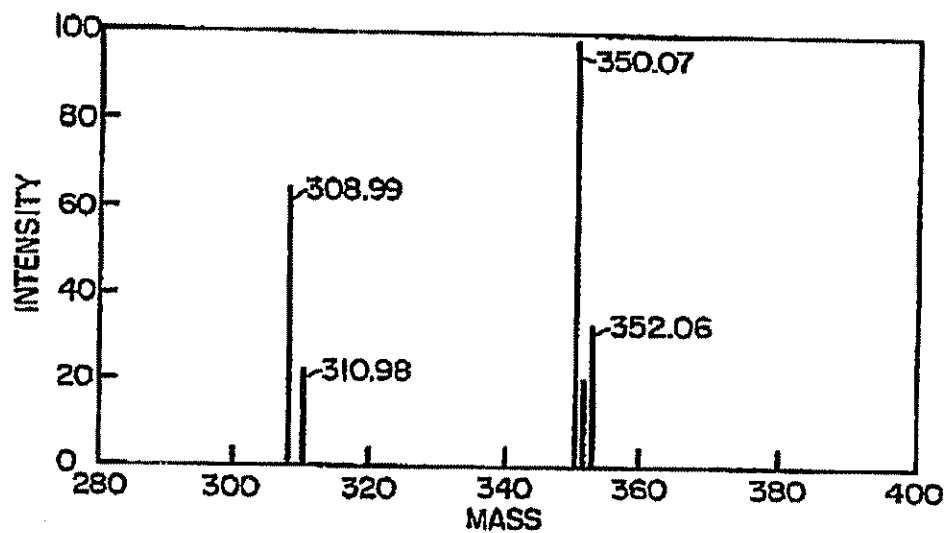
FIG_2B

U.S. Patent

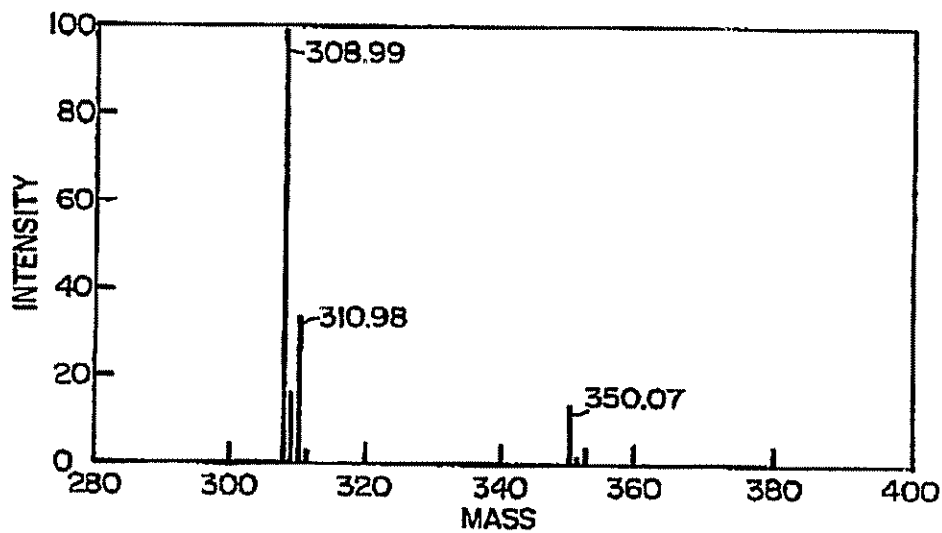
Mar. 4, 2003

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FIG_3A



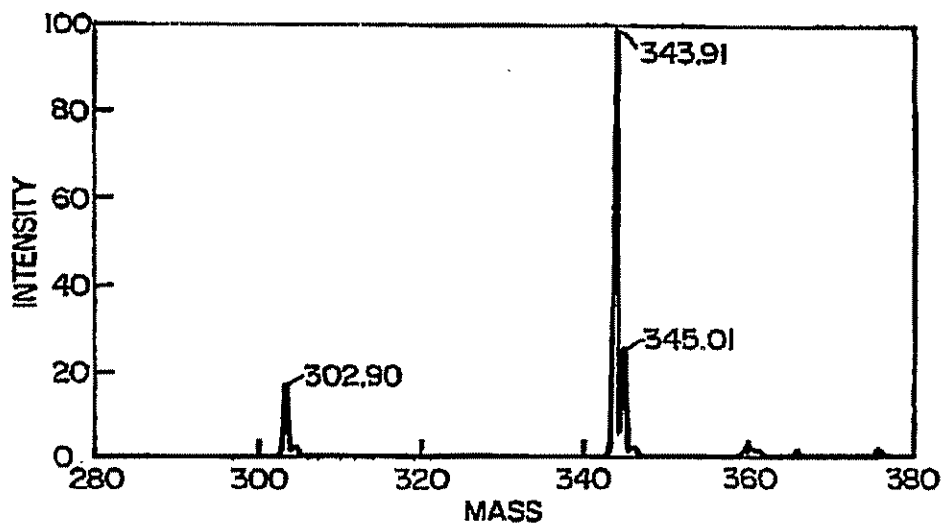
FIG_3B

U.S. Patent

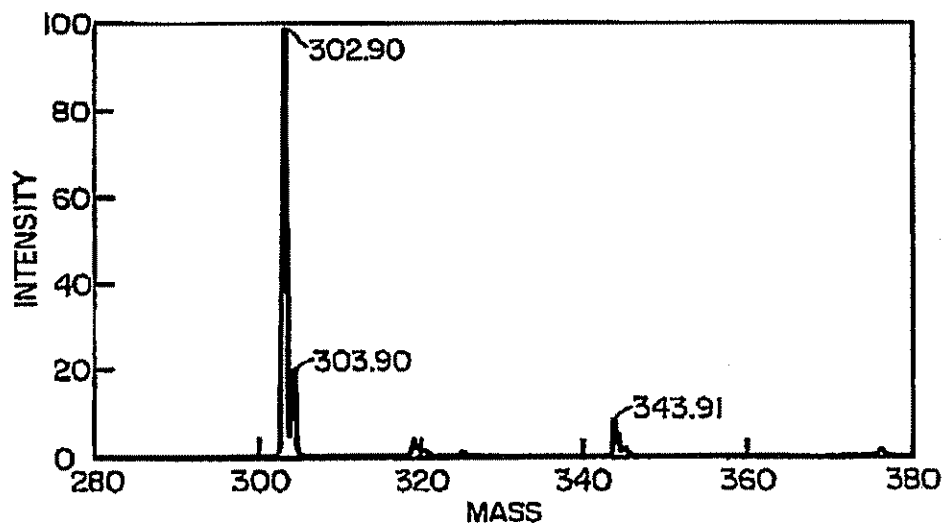
Mar. 4, 2003

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FIG_4A



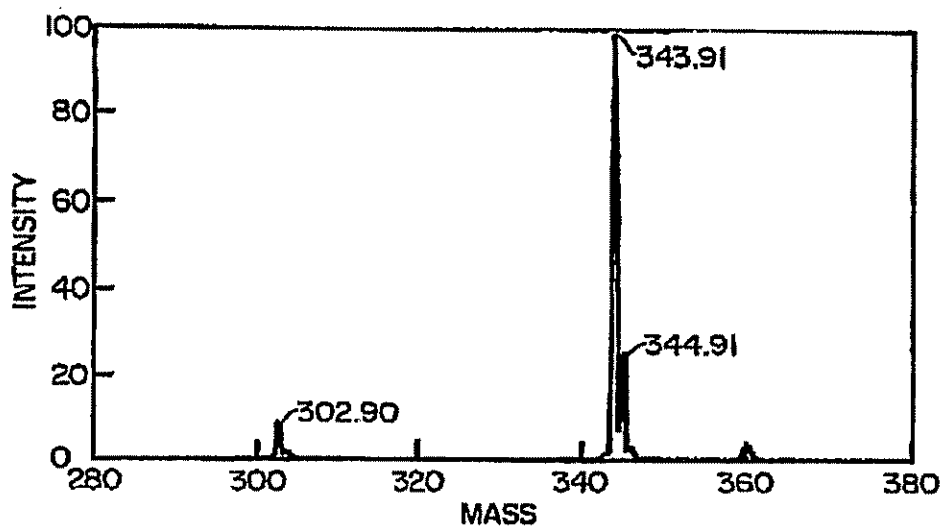
FIG_4B

U.S. Patent

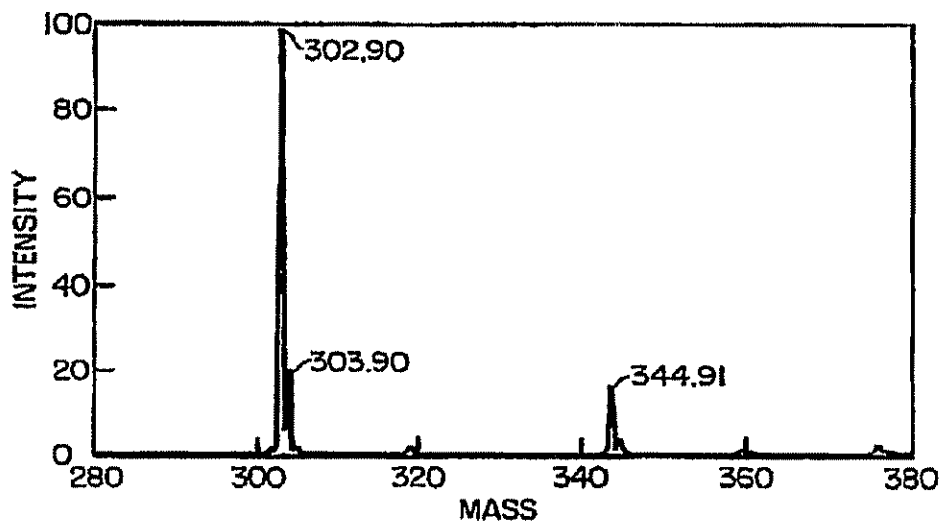
Mar. 4, 2003

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FIG_5A



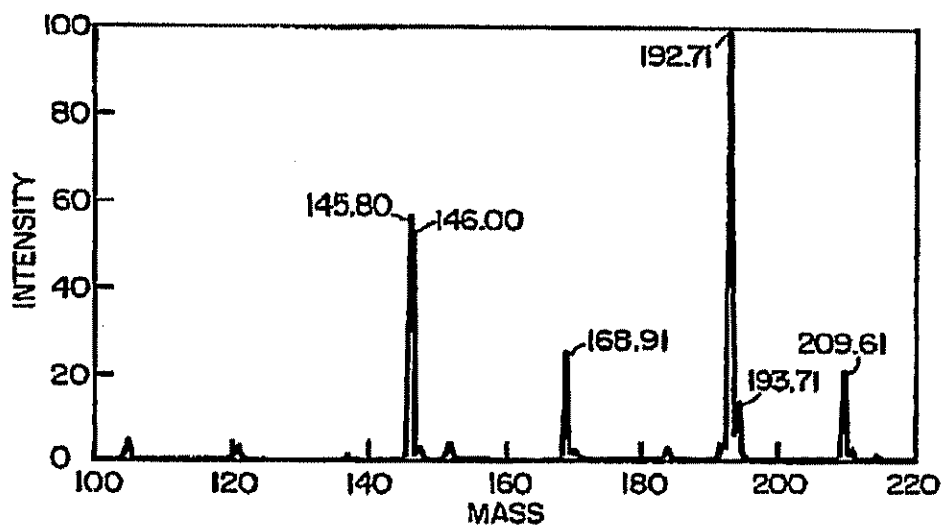
FIG_5B

U.S. Patent

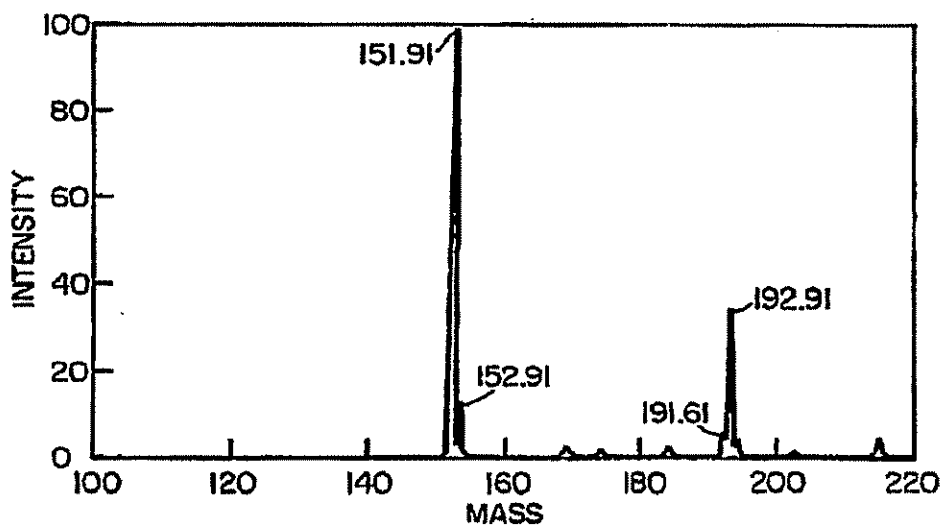
Mar. 4, 2003

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FIG_6A



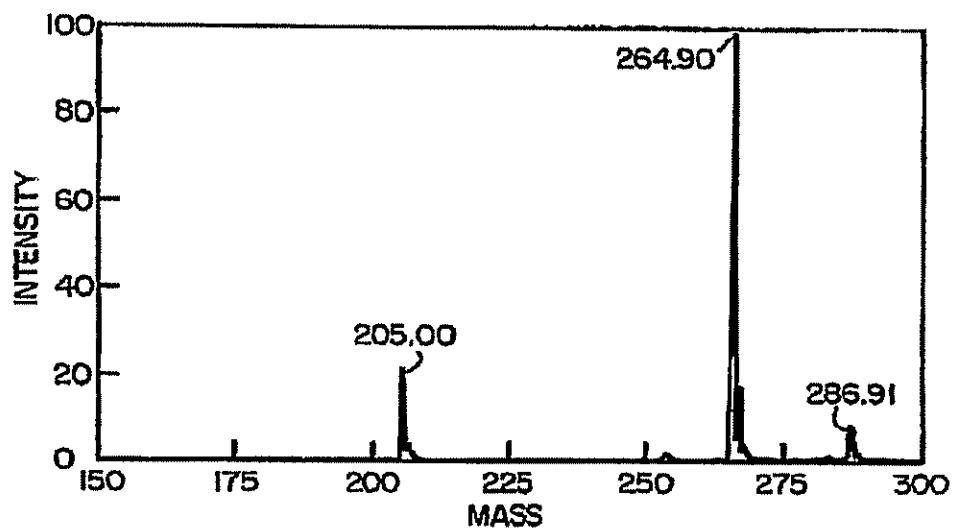
FIG_6B

U.S. Patent

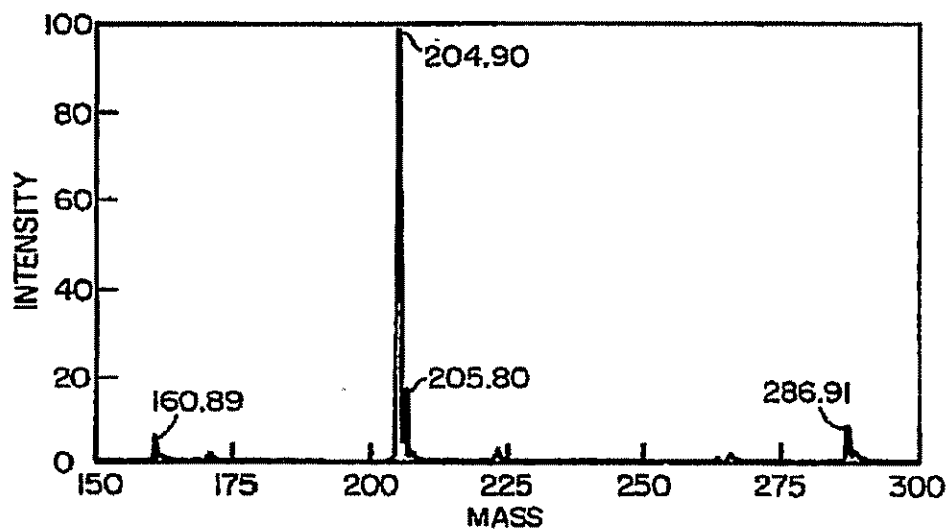
Mar. 4, 2003

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FIG_7A



FIG_7B

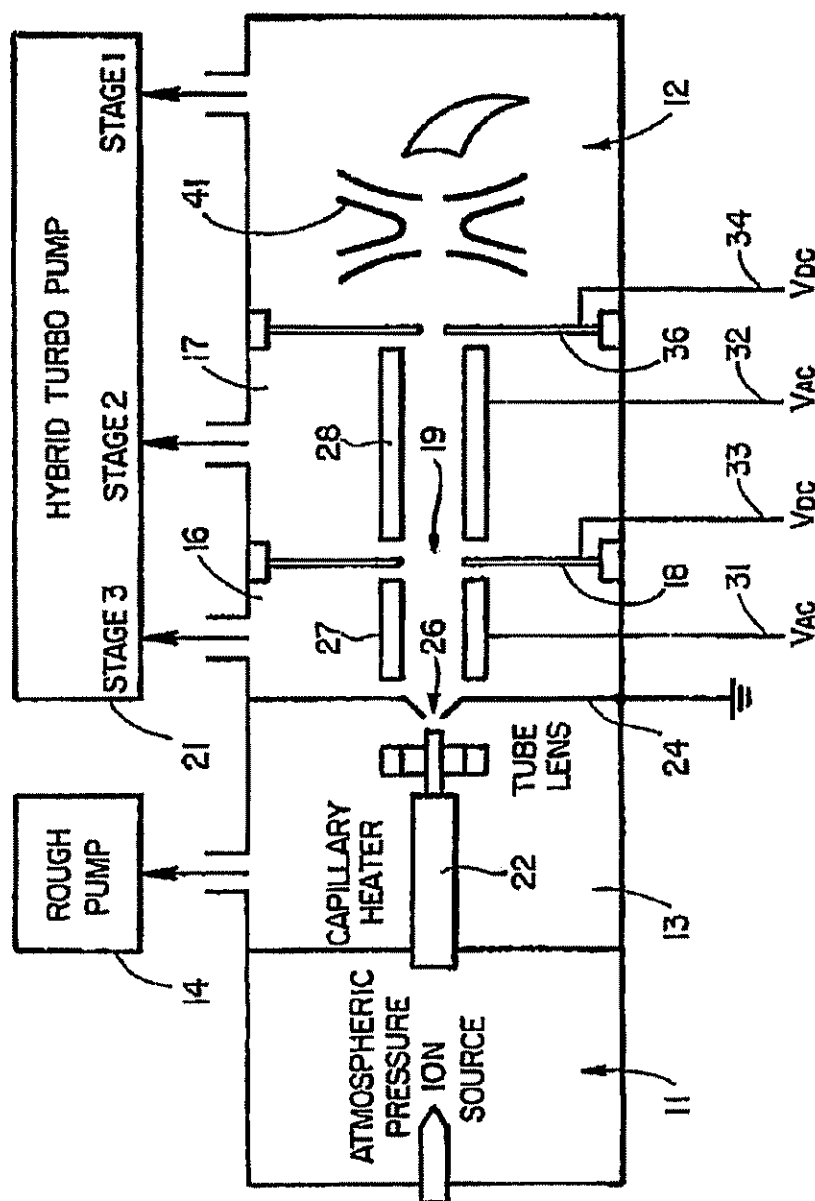


FIG-8

PTO/SB/51 (09-04)

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REISSUE APPLICATION DECLARATION BY THE INVENTOR

Docket Number (Optional)

102718-300

I hereby declare that:

Each inventor's residence, mailing address and citizenship are stated below next to their name.

I believe the inventors named below to be the original and first inventor(s) of the subject matter which is described and claimed in patent number 6,528,784, granted 3/4/2003 and for which a reissue patent is sought on the invention entitled Mass Spectrometer System Including a Double Ion Guide Interface and Method of Operation

the specification of which

☒ is attached hereto.☐ was filed on _____ as reissue application number _____and was amended on _____
(If applicable)

I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR 1.56.

☐ I hereby claim foreign priority benefits under 35 U.S.C. 119(a)-(d) or (f), or 365(b). Attached is form PTO/SB/02B (or equivalent) listing the foreign applications.

I verily believe the original patent to be wholly or partly inoperative or invalid, for the reasons described below. (Check all boxes that apply.)

☐ by reason of a defective specification or drawing.☒ by reason of the patentee claiming more or less than he had the right to claim in the patent.☐ by reason of other errors.

At least one error upon which reissue is based is described below. If the reissue is a broadening reissue, such must be stated with an explanation as to the nature of the broadening:

This is an application for broadened reissue. Claim 1 of the patent claims the apparatus invention of the patent too narrowly with the result that the patentees claimed less than they had the right to claim. In newly-presented Claim 16, the phrase "increasing the translational kinetic energy" as appears in Claim 1 has been changed to "defining the translational kinetic energy", resulting in a broader literal scope than original Claim 1 of the patent. Furthermore, for example, newly-presented Claim 10 does not require "first and second evacuated chambers" as is recited in original Claim 1, and Claim 10 also recites "defining" the energy rather than "increasing" the energy as recited in original Claim 1.

[Page 1 of 2]

This collection of information is required by 37 CFR 1.175. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 30 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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PTO/SB/51 (09-04)


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(REISSUE APPLICATION DECLARATION BY THE INVENTOR, page 2)		Docket Number (Optional) 102718-300	
All errors corrected in this reissue application arose without any deceptive intention on the part of the applicant			
Note: To appoint a power of attorney, use form PTO/SB/81.			
Correspondence Address: Direct all communications about the application to:			
<input checked="" type="checkbox"/> The address associated with Customer Number:			
OR			
<input type="checkbox"/> Firm or Individual Name			
Address			
City	State	Zip	
Country			
Telephone	Fax		
I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine and imprisonment, or both, under 18 U.S.C. 1001, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this declaration is directed.			
Full name of sole or first inventor (given name, family name) Keqi Tang			
Inventor's signature		Date	
Residence 324 Snyder St., Richland, WA 99354		Citizenship U.S.A.	
Mailing Address			
Full name of second joint inventor (given name, family name) Jean-Jacques Dunyach			
Inventor's signature		Date	
Residence 1898 Cleveland Avenue San Jose, CA 95126		Citizenship France	
Mailing Address			
Full name of third joint inventor (given name, family name) Alan E. Schoen			
Inventor's signature		Date	
Residence 16810 Bohlmon Road Saratoga, CA 95070		Citizenship U.S.A.	
Mailing Address			
<input type="checkbox"/> Additional joint inventors or legal representative(s) are named on separately numbered sheets forms PTO/SB/02A or 02LR attached hereto.			

PTO/SB/53 (04-04)
Approved for use through 04/30/2007. OMB 0651-0033
U.S. Patent and Trademark Office; U.S. DEPARTMENT OF COMMERCE
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REISSUE APPLICATION: CONSENT OF ASSIGNEE; STATEMENT OF NON-ASSIGNMENT		Docket Number (Optional) 102718-300
This is part of the application for a reissue patent based on the original patent identified below.		
Name of Patentee(s) Keqi Tang, et al.		
Patent Number 6,528,784	Date Patent Issued March 4, 2003	
Title of Invention Mass Spectrometer System Including A Double Ion Guide Interface and method of operation		
<p>1. <input checked="" type="checkbox"/> Filed herein is a statement under 37 CFR 3.73(b). (Form PTO/SB/96)</p> <p>2. <input type="checkbox"/> Ownership of the patent is in the inventor(s), and no assignment of the patent is in effect.</p> <p>One of boxes 1 or 2 above must be checked. If multiple assignees, complete this form for each assignee. If box 2 is checked, skip the next entry and go directly to "Name of Assignee".</p> <p>The written consent of all assignees and inventors owning an undivided interest in the original patent is included in this application for reissue.</p>		
The assignee(s) owning an undivided interest in said original patent is/are <u>Thermo Finnigan LLC</u> and the assignee(s) consents to the accompanying application for reissue.		
Name of assignee/inventor (if not assigned) Thermo Finnigan LLC		
Signature 	Date March 1, 2005	
Typed or printed name and title of person signing for assignee (if assigned) Seth H. Hoogasian President and Secretary		

This collection of information is required by 37 CFR 1.172. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 6 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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PTO/SB/96 (09-04)

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STATEMENT UNDER 37 CFR 3.73(b)Applicant/Patent Owner: Thermo Finnigan LLCApplication No./Patent No.: 6,528,784 Filed/Issue Date: March 4, 2003Entitled: **Mass Spectrometer System including a Double Ion Guide Interface and method of operation**Thermo Finnigan LLC, a Delaware limited liability company
(Name of Assignee) (Type of Assignee, e.g., corporation, partnership, university, government agency, etc.)

states that it is:

1. ☒ the assignee of the entire right, title, and interest; or
2. ☐ an assignee of less than the entire right, title and interest.
The extent (by percentage) of its ownership interest is _____ %

in the patent application/patent identified above by virtue of either:

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

OR

B. ☒ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as shown below:1. From: Inventors To: Finnigan CorporationThe document was recorded in the United States Patent and Trademark Office at
Reel 011718, Frame 0914, or for which a copy thereof is attached.2. From: Finnigan Corporation To: Thermo Finnigan LLCThe document was recorded in the United States Patent and Trademark Office at
Reel 011898, Frame 0886, or for which a copy thereof is attached.

3. From: _____ To: _____

The document was recorded in the United States Patent and Trademark Office at
Reel _____, Frame _____, or for which a copy thereof is attached.☐ Additional documents in the chain of title are listed on a supplemental sheet.☐ Copies of assignments or other documents in the chain of title are attached.

[NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, if the assignment is to be recorded in the records of the USPTO. See MPEP 302.08]

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Seth H. Hoogasian

Signature

Printed or Typed Name

President and Secretary

Title

March 1, 2005

Date

(781) 622-1000

Telephone Number

This collection of information is required by 37 CFR 3.73(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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PTO/SB/81 (11-04)

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**POWER OF ATTORNEY
and
CORRESPONDENCE ADDRESS
INDICATION FORM**

Application Number	Reissue of US 6, 528,784
Filing Date	Concurrently herewith
First Named Inventor	Keqi Tang et al.
Title	Mass Spectrometer....
Art Unit	N/A
Examiner Name	N/A
Attorney Docket Number	102718-300

I hereby revoke all previous powers of attorney given in the above-identified application.

I hereby appoint:

☒ Practitioners associated with the Customer Number:

27267

OR

☐ Practitioner(s) named below:

Name	Registration Number

as my/our attorney(s) or agent(s) to prosecute the application identified above, and to transact all business in the United States Patent and Trademark Office connected therewith.

Please recognize or change the correspondence address for the above-identified application to:

☐ The address associated with the above-mentioned Customer Number:

OR

☐ The address associated with Customer Number:

OR

<input type="checkbox"/> Firm or Individual Name			
Address			
City	State	Zip	
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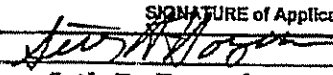
I am the:

☐ Applicant/Inventor.

☒ Assignee of record of the entire interest. See 37 CFR 3.71.

Statement under 37 CFR 3.73(b) is enclosed. (Form PTO/SB/96)

SIGNATURE of Applicant or Assignee of Record

Signature		Date	March 1, 2005
Name	Seth H. Hoogasian	Telephone	(781)622-1000
Title and Company	President and Secretary, Thermo Finnigan LLC		

NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.

☒ *Total of 2 forms are submitted.

This collection of information is required by 37 CFR 1.31, 1.32 and 1.33. The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 3 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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STATEMENT UNDER 37 CFR 3.73(b)

Applicant/Patent Owner: Thermo Finnigan LLCApplication No./Patent No.: 6,528,784 Filed/Issue Date: March 4, 2003Entitled: Mass Spectrometer System including a Double Ion Guide Interface and method of operationThermo Finnigan LLC, a Delaware limited liability company
(Name of Assignee) (Type of Assignee: e.g., corporation, partnership, university, government agency, etc.)

states that it is:

1. ☒ the assignee of the entire right, title, and interest; or
2. ☐ an assignee of less than the entire right, title and interest.
The extent (by percentage) of its ownership interest is _____ %

In the patent application/patent identified above by virtue of either:

A. ☐ An assignment from the inventor(s) of the patent application/patent identified above. The assignment was recorded in the United States Patent and Trademark Office at Reel _____, Frame _____, or for which a copy thereof is attached.

OR

B. ☒ A chain of title from the inventor(s), of the patent application/patent identified above, to the current assignee as shown below:1. From: Inventors To: Finnigan CorporationThe document was recorded in the United States Patent and Trademark Office at
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Reel _____, Frame _____, or for which a copy thereof is attached.☐ Additional documents in the chain of title are listed on a supplemental sheet.☐ Copies of assignments or other documents in the chain of title are attached.

(NOTE: A separate copy (i.e., a true copy of the original assignment document(s)) must be submitted to Assignment Division in accordance with 37 CFR Part 3, if the assignment is to be recorded in the records of the USPTO. See MPEP 302.08)

The undersigned (whose title is supplied below) is authorized to act on behalf of the assignee.

Seth H. Hoogasian
Signature

Printed or Typed Name

President and Secretary

Title

March 1, 2005
Date(781) 622-1000

Telephone Number

This collection of information is required by 37 CFR 3.73(b). The information is required to obtain or retain a benefit by the public which is to file (and by the USPTO to process) an application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.11 and 1.14. This collection is estimated to take 12 minutes to complete, including gathering, preparing, and submitting the completed application form to the USPTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden, should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, P.O. Box 1450, Alexandria, VA 22313-1450. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application : Keqi Tang et al.
Serial No. : Concurrently-filed application for Reissue Patent
Patent No. : 6,528,784 (Ser. No. 09/715,815, filed November 16, 2000,
issued March 4, 2003)
Filed : Herewith
For : MASS SPECTROMETER SYSTEM INCLUDING A
DOUBLE ION GUIDE INTERFACE AND METHOD OF
OPERATION
Assignee : Thermo Finnigan LLC
Attorney Docket : 102718-300
Customer No. : 27267

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By 
Elizabeth A. Galletta

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Commissioner for Patents
P.O. BOX 1450
Alexandria, VA 22313-1450

PRELIMINARY AMENDMENT UNDER 37 CFR §1.173(b)

Sir:

In connection with the above-referenced Reissue application filed concurrently herewith, please enter the following amendments and remarks:

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application : Keqi Tang et al.
Serial No. : Concurrently-filed application for Reissue Patent
Patent No. : 6,528,784 (Ser. No. 09/715,815, filed Nov. 16, 2000, issued
Mar. 4, 2003)
Filed : Herewith
For : MASS SPECTROMETER SYSTEM INCLUDING A
DOUBLE ION GUIDE INTERFACE AND METHOD OF
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Assignee : Thermo Finnigan LLC
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By 
Elizabeth A. Galletta

MAIL STOP REISSUE
Commissioner for Patents
P.O. BOX 1450
Alexandria, VA 22313-1450

STATEMENT UNDER 37 CFR §1.178(b)

Sir:

In connection with the above-referenced Reissue patent application, Applicants wish to indicate to the Examiner that the U.S. Patent No. 6,528,784 for which reissue is sought is currently in litigation. The litigation is entitled *Thermo Finnigan LLC v. Applera Corporation*, Civil Action No. 1:05-cv-00110, filed in the U.S. District Court, District of Delaware on February 23, 2005.

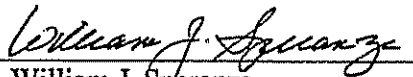
Despite the existence of this litigation, Applicants request that action in this Reissue application proceed, as it is the Applicants' desire to have the Reissue application be examined at this time.

If the Examiner has any questions, the Examiner is invited and encouraged to contact Applicant's representative at the telephone number listed below.

Date: March 4, 2005

Respectfully submitted,

Keqi Tang, et al.

By 

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In the Claims:

Please add new Claims 10 through 42, for inclusion as part of this Reissue application as filed, as follows:

Claim 10. (New) A mass spectrometer system, comprising:

an ion source for creating sample ions at atmospheric pressure from a sample which is in association with a solvent;

a mass analyzer, disposed in a high vacuum mass analyzer chamber, for analyzing said sample ions;

two consecutive multipole ion guides disposed between said ion source and said high vacuum mass analyzer chamber for directing ions from said ion source to said high vacuum mass analyzer chamber, said multipole ion guides maintained at a pressure below atmospheric but higher than the pressure of said high vacuum mass analyzer chamber; and

at least one of said multipole ion guides having means associated therewith for defining the translational kinetic energy of ions directed therethrough, and wherein said translational kinetic energy is chosen so that solvent adduct species formed in high pressure regions of the system are converted within said multipole ion guides to sample ions by collision-induced dissociation without fragmentation of sample ions before entering said high vacuum mass analyzer chamber.

Claim 11. (New) The mass spectrometer system of Claim 10 wherein said means is for increasing said translational kinetic energy.

Claim 12. (New) The mass spectrometer system of Claim 10 wherein said two consecutive multipole ion guides are contained, respectively, in two consecutive evacuated chambers.

Claim 13. (New) The mass spectrometer system of Claim 12 wherein the first evacuated chamber containing the first of said multipole ion guides is at a pressure greater than the pressure in the second evacuated chamber containing the second of said multipole ion guides.

Claim 14. (New) The mass spectrometer system of Claim 10 wherein said mass analyzer is a tandem mass analyzer.

Claim 15. (New) The mass spectrometer system of Claim 10 wherein said mass analyzer is a quadrupole ion trap mass analyzer.

Claim 16. (New) A mass spectrometer system including a mass analyzer disposed in a high vacuum chamber for analyzing sample ions formed at atmospheric pressure and directed to the analyzer through intermediate vacuum chambers in which sample ions and solvent molecules form adduct ions with a reduction of sample ion current including:

first and second evacuated chambers directly preceding the mass analyzer chamber with the first chamber being at a higher pressure than the second chamber,

a first multipole ion guide in the first chamber for guiding ions into said second chamber,

a second multipole ion guide in the second chamber for guiding ions from the first chamber into the high vacuum chamber for mass analysis, and

means associated with one or both of said first and second multipole ion guides for defining the translational kinetic energy of the adduct ions so that at the vacuum pressure of the second interface chamber adduct ions traveling into the chamber are converted into sample ions without fragmentation of the sample ions whereby to increase the sample ion current and therefore the sensitivity of the mass spectrometer system.

Claim 17. (New) A mass spectrometer system including a mass analyzer disposed in a high vacuum chamber for analyzing sample ions formed at atmospheric pressure and directed to the analyzer through one or more intermediate vacuum chambers in which sample ions and solvent molecules form adduct ions with a reduction of sample ion current including:

first and second multipole ion guides disposed consecutively in said one or more intermediate vacuum chambers, with said first multipole ion guide maintained at a higher pressure than said second multipole ion guide, for directing ions into the high vacuum chamber for mass analysis, and

means associated with one or both of said first and second multipole ion guides for defining the translational kinetic energy of the adduct ions directed therethrough so that at the

pressure of said one or both ion guides adduct ions traveling therethrough are converted into sample ions without fragmentation of the sample ions whereby to increase the sample ion current and therefore the sensitivity of the mass spectrometer system.

Claim 18 (New) A mass spectrometer system according to Claim 17 wherein said means is for increasing said translational kinetic energy.

Claim 19. (New) A mass spectrometer system, including:

- A. an ion source for creating ions from a sample which is in association with a solvent;
- B. a first chamber, a second chamber, and a tandem mass analyzer, the first chamber being disposed between the ion source and the second chamber, the second chamber being disposed between the first chamber and the tandem mass analyzer, the first chamber being evacuated to a first pressure, the second chamber being evacuated to a second pressure;
- C. a first multipole ion guide disposed in the first chamber for guiding ions received in the first chamber towards the second chamber;
- D. a second multipole ion guide disposed in the second chamber for guiding ions received in the second chamber towards the tandem mass analyzer, at least some of the ions in the second chamber being a solvent adduct species;
- E. a lens disposed between the first and second multipole ion guides, a voltage difference between the lens and the second multipole ion guide defining a kinetic energy of ions in the second chamber, the kinetic energy being sufficient to dissociate the sample from the solvent in the solvent adduct species without causing fragmentation of the sample ions.

Claim 20. (New) A mass spectrometer system according to Claim 19 wherein the kinetic energy is sufficient to dissociate the sample from the solvent in the solvent adduct species in a majority of the solvent adduct species.

Claim 21. (New) A mass spectrometer system according to Claim 20 wherein the solvent adduct species includes one sample ion and one solvent molecule.

Claim 22. (New) A mass spectrometer system according to Claim 20 wherein the solvent adduct species includes one sample ion and one solvent ion.

Claim 23. (New) A mass spectrometer system according to Claim 20 wherein the ion source is an electrospray ion source.

Claim 24. (New) A mass spectrometer according to Claim 23 wherein the ion source is an atmospheric pressure electrospray ion source.

Claim 25. (New) A mass spectrometer system according to Claim 20 wherein the ion source is an atmospheric pressure chemical ionization source.

Claim 26. (New) A mass spectrometer system according to Claim 20, the tandem mass analyzer including a Q1 stage, a Q2 stage, a Q3 stage, and a detector, the Q1 stage including a first multipole rod structure, the Q2 stage including a second multipole rod structure, and the Q3 stage including a third multipole rod structure.

Claim 27. (New) A mass spectrometer system according to Claim 20, the first pressure being higher than the second pressure.

Claim 28. (New) A mass spectrometer system according to Claim 20, the first ion guide being a quadrupole ion guide.

Claim 29. (New) A mass spectrometer system according to Claim 20, the second ion guide being a quadrupole ion guide.

Claim 30. (New) A mass spectrometer system, including:

- A. an ion source for creating ions from a sample which is in association with a solvent;
- B. a first chamber, a second chamber, and a tandem mass analyzer, the first chamber being disposed between the ion source and the second chamber, the second chamber being disposed between the first chamber and the tandem mass analyzer, the first chamber being evacuated to a first pressure, the second chamber being evacuated to a second pressure;
- C. a first multipole ion guide disposed in the first chamber for guiding ions received in the first chamber towards the second chamber;
- D. a second multipole ion guide disposed in the second chamber for guiding ions received in the second chamber towards the tandem mass analyzer, at least some of the ions in the second chamber being a solvent adduct species;
- E. a first lens disposed between the first and second multipole ion guides, and a second lens disposed between the ion source and the first multipole ion guide, a voltage difference between the first or second lenses and the second multipole ion guide defining a kinetic energy of ions in the second chamber, the kinetic energy being sufficient to dissociate the sample from the solvent in the solvent adduct species without causing fragmentation of the sample ions.

Claim 31. (New) A mass spectrometer system, including:

- A. an ion source for creating ions from a sample which is in association with a solvent;
- B. a first chamber, a second chamber, and a tandem mass analyzer, the first chamber being disposed between the ion source and the second chamber, the second chamber being disposed between the first chamber and the tandem mass analyzer, the first chamber being evacuated to a first pressure, the second chamber being evacuated to a second pressure;
- C. a first multipole ion guide disposed in the first chamber for guiding ions received in the first chamber towards the second chamber;
- D. a second multipole ion guide disposed in the second chamber for guiding ions received in the second chamber towards the tandem mass analyzer, at least some of the ions in the second chamber being a solvent adduct species;
- E. a lens disposed between the first and second multipole ion guides, a voltage difference between the lens and the second multipole ion guide increasing a kinetic energy of ions in the second chamber, the kinetic energy being sufficient to dissociate the sample from the solvent in the solvent adduct species without causing fragmentation of the sample ions.

Claim 32. (New) A mass spectrometer system according to Claim 31 wherein the kinetic energy is sufficient to dissociate the sample from the solvent in the solvent adduct species in a majority of the solvent adduct species.

Claim 33. (New) A mass spectrometer system according to Claim 32 wherein the solvent adduct species includes one sample ion and one solvent molecule.

Claim 34. (New) A mass spectrometer system according to Claim 32 wherein the solvent adduct species includes one sample ion and one solvent ion.

Claim 35. (New) A mass spectrometer system according to Claim 32 wherein the ion source is an electrospray ion source.

Claim 36. (New) A mass spectrometer according to Claim 35 wherein the ion source is an atmospheric pressure electrospray ion source.

Claim 37. (New) A mass spectrometer system according to Claim 32 wherein the ion source is an atmospheric pressure chemical ionization source.

Claim 38. (New) A mass spectrometer system according to Claim 32, the tandem mass analyzer including a Q1 stage, a Q2 stage, a Q3 stage, and a detector, the Q1 stage including a first multipole rod structure, the Q2 stage including a second multipole rod structure, and the Q3 stage including a third multipole rod structure.

Claim 39. (New) A mass spectrometer system according to Claim 32, the first pressure being higher than the second pressure.

Claim 40. (New) A mass spectrometer system according to Claim 32, the first ion guide being a quadrupole ion guide.

Claim 41. (New) A mass spectrometer system according to Claim 32, the second ion guide being a quadrupole ion guide.

Claim 42. (New) A mass spectrometer system, including:

A. an ion source for creating ions from a sample which is in association with a solvent;

B. a first chamber, a second chamber, and a tandem mass analyzer, the first chamber being disposed between the ion source and the second chamber, the second chamber being disposed between the first chamber and the tandem mass analyzer, the first chamber being evacuated to a first pressure, the second chamber being evacuated to a second pressure;

C. a first multipole ion guide disposed in the first chamber for guiding ions received in the first chamber towards the second chamber;

D. a second multipole ion guide disposed in the second chamber for guiding ions received in the second chamber towards the tandem mass analyzer, at least some of the ions in the second chamber being a solvent adduct species;

E. a first lens disposed between the first and second multipole ion guides, and a second lens disposed between the ion source and the first multipole ion guide, a voltage difference between the first or second lenses and the second multipole ion guide increasing a kinetic energy of ions in the second chamber, the kinetic energy being sufficient to dissociate the sample from the solvent in the solvent adduct species without causing fragmentation of the sample ions.

REMARKS

The foregoing amendments add new Claims 10 through 42 to the concurrently-filed application for broadening reissue of U.S. Patent No. 6,528,784, issued March 4, 2003, and should be entered in the application as part of the reissue application as filed.

STATEMENT UNDER 37 C.F.R. 1.173(c)

As required by 37 C.F.R. 1.173(c), the following is the information with respect to the status of all claims in this application and the support for newly-added claims.

Status of Application Claims

U.S. Patent No. 6,528,784 (the '784 Patent) issued on March 4, 2003 containing Claims 1 through 9. Those claims are repeated verbatim in this concurrently-filed application for broadened reissue of the '784 Patent and are thus part of this Reissue application and are pending herein. The Preliminary Amendment herein adds new Claims 10 through 42 for consideration in the reissue application, and are to be considered as part of the reissue application as concurrently filed herewith.

Thus, in this reissue application, Claims 1 through 42 are pending.

Support for Newly-Added Claims

New Claim 10, an independent claim, finds support throughout the specification, claims and drawings of the '784 Patent as issued on March 4, 2003. The claim elements of Claim 10 find support as set forth below, it being understood that the following are simply examples of where such support is found and are presented without prejudice to reliance upon other portions of the specification, claims and drawings of the '784 Patent for such support should that be required in future proceedings.

"A mass spectrometer system"

That the invention is directed to a mass spectrometer system is set forth in *ipsis verbis* at Column 2, lines 64-65, and in Claim 1 (Column 7, line 12)

"An ion source for creating sample ions at atmospheric pressure"

An "atmospheric pressure ion source is shown as element 11 in FIGS. 1 and 8, and described at Column 4, lines 53-57

"From a sample in association with a solvent"

The '784 Patent contains numerous references to, and the invention thereof is directed to, the problem of the formation of adduct ions from sample ions and "solvent molecules," such as at Column 2, lines 37-51, Column 5, lines 11-19

"A mass analyzer, disposed in a high vacuum mass analyzer chamber, for analyzing said sample ions"

See element 12 in each of FIGS. 1 and 8. Column 3, lines 5-7

"Two consecutive multipole ion guides disposed between said ion source and said high vacuum mass analyzer chamber for directing ions from said ion source to said high vacuum mass analyzer chamber"

Each of FIGS. 1 and 8 shows two multipole ion guides, 27, 28 arranged between ion source 11 and mass analyzer chamber 12. At Column 4, lines 64-66, it is noted that ions from the source "are guided into the mass analyzer by first and second multipole ion guides. See also the Column 1, lines 14-18, and the Abstract

"Said multipole ion guides being maintained at a pressure below atmospheric but higher than the pressure of said high vacuum mass analyzer chamber"

See, Column 4, lines 32-52 providing values for pressure, including the atmospheric pressure of the ion source, the high vacuum of the mass analyzer chamber, and the pressures at which the ion guides operate as being therebetween

"At least one of said multipole ion guides having means associated therewith for defining the translational kinetic energy of ions directed there-through"

Claim 1, Column 7, lines 26-27; Column 3, lines 27-30 (potential difference defines the ion's translational kinetic energy)

"And wherein said translational kinetic energy is chosen so that solvent adduct species formed in high pressure

Col. 3, lines 31-38; Col. 1, lines 14-18; Abstract; Col. 5, lines 11-12; Claim 1 (conversion of adduct ions to sample

regions of the system are converted within said multipole ion guides to sample ions by collision-induced dissociation without fragmentation of sample ions before entering said high vacuum mass analyzer chamber”

ions to increase sample ion current and sensitivity of mass spectrometer); Column 3, lines 33-38 (adduct ions converted to sample ions by collision-induced dissociation without fragmentation); Col. 2, line 47 (solvent adduct species)

Claim 11 finds support at, e.g., Column 5, lines 22-24, reciting that the means increases the translational kinetic energy of ions.

Claim 12 finds support at, e.g., Column 3, lines 7-13; FIGS. 1 and 8; and Claim 1 of the ‘784 Patent.

Claim 13 finds support at Column 3, lines 9-10 (first interface chamber being at a higher pressure than the second interface chamber).

Claim 14 finds explicit support at Column 3, lines 64-67 and FIG. 1, showing a tandem mass spectrometer.

Claim 15 finds explicit support at Column 7, lines 5-7, where it is indicated that a quadrupole ion trap may be used as the mass analyzer.

Claim 16 is identical to Claim 1 of the ‘784 Patent, but broadened by reason of substitution of “defining” the translational kinetic energy of the ions for the terminology “increasing” the translational kinetic energy of the ions. Support for this change, and thus for a claim of this breadth, is as found, e.g., at Column 3, lines 27-31 (potential difference “defines the ion’s translational kinetic energy” as it enters ion guide).

Claim 17 contains the same change from Claim 1 of the ‘784 Patent as in Claim 16 insofar as the “defining” terminology, and thus finds support as there noted. Claim 17 further eliminates the requirement of Claim 1 for two separate vacuum chambers, each containing a multipole ion guide, instead reciting merely that there are two consecutive multipole ion guides under vacuum conditions, whether in separate vacuum chambers or a single vacuum chamber or the like. Support for these changes, and thus for a claim of this breadth, is found, for example, in the Abstract and at Column 1, lines 14-18, where the statement of the invention is simply that two consecutive multipole ion guides between the ion source and the mass analyzer are used to dissociate adduct ions so as to increase sample ion current.

~~Claim 18 finds support at Column 5, lines 22-24.~~

Claim 19 is a new independent claim. Support for the recitation of an “ion source” as an element in the mass spectrometer system and the creation of ions from a sample “in association with a solvent” is as recited above with respect to new Claim 10. The recitation of first and second chambers and a mass analyzer is the same as set forth in Claim 1 of the ‘784 Patent, and the recital that the mass analyzer is a “tandem mass analyzer” is supported by the specification at Column 3, lines 64-67 and FIG. 1, showing a tandem mass spectrometer. That the first and second chambers are evacuated and arranged as claimed, namely, the first chamber disposed between the ion source and the second chamber and the second chamber disposed between the first chamber and the mass analyzer is supported at, e.g. FIGS. 1 and 8 and Claim 1 of the ‘784 Patent (the vacuum chambers are “intermediate vacuum chambers relative to the ion source and the mass analyzer”). The presence of a first multipole ion guide in the first chamber and a second multipole ion guide in the second chamber and their respective functions in guiding ions from recited chambers is supported, e.g., by Claim 1 of the ‘784 Patent, FIGS. 1 and 8, and Column 3, lines 9-15. That some of the ions are solvent adducts species is supported, e.g., at Column 2, lines 39-47. A lens between the first and second ion guides is shown in FIGS. 1 and 8 (element 18) and at Column 3, lines 19-22 (interchamber lens disposed between first and second interface chambers). A voltage difference between the lens and the second multipole ion guide is recited, e.g., in FIGS. 1 and 8 (V_{DC} 33), at Column 3, lines 27-30 (potential difference between interchamber lens and the second multipole ion guide). That the potential difference defines a kinetic energy of ions in the second chamber is stated at Column 3, lines 30-31. The selection of kinetic energy sufficient to dissociate adduct ions without causing fragmentation is disclosed at Column 3, lines 32-35 and Claim 1 of the ‘784 Patent.

Dependent Claim 20 is supported, e.g., by FIGS. 2 through 7 of the ‘784 Patent, and Table 2, showing dissociation of the sample from the solvent in a majority of the solvent adduct species.

Dependent Claim 21 is supported, e.g., by Column 2, lines 39-47 and lines 55-56.

Dependent Claim 22 is supported, e.g., by Column 2, lines 39-47, 55-56.

Dependent Claims 23 and 24 are supported by, e.g., FIGS. 1 and 8 (element 11, atmospheric pressure ion source) and Column 4, lines 32-33.

Dependent Claim 25 is supported by Column 4, lines 53-55 (atmospheric pressure chemical ionization source).

Dependent Claim 26 is supported by FIG. 1 and its description at Column 3, lines 64-67 (tandem mass analyzer), and the Q1, Q2 and Q3 notations in FIG. 1, and the reference to the TSQ 7000 instrument at Column 5, lines 34-35.

Dependent Claim 27 is supported at, e.g., Column 3, lines 9-10 (first interface chamber being at a higher pressure than the second interface chamber).

Dependent Claim 28 is supported at, e.g., Column 4, line 66 to Column 5, line 4. The same disclosure provides support for dependent Claim 29.

New independent Claim 30 is supported in the same manner as Claim 19. The further recitation of a lens between the ion source and the first mutipole ion guide, and a potential difference between the first or second lenses and the second ion guide, is supported by FIGS. 1 and 8, the disclosure at Column 3, lines 17-22, 27-30.

New independent Claim 31 and Claims 32-41 dependent thereon and new independent Claim 42 parallel Claims 19-30, with recitation that the potential difference increases the kinetic energy of ions, support for which is found in Column 5, lines 22-24.

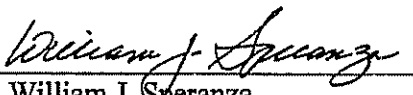
In all the foregoing, just as noted in respect of Claim 10, the recitations of where support may be found for the new claims are presented as examples and without prejudice to reliance upon other portions of the '784 Patent for such support in the event such may be required.

If the Examiner has any questions, the Examiner is invited and encouraged to contact Applicant's representative at the telephone number listed below.

Date: March 4, 2005

Respectfully submitted,

Keqi Tang, et al.

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